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Pan-immune inflammation value as a biomarker in ankylosing spondilitis and associated with disease activity

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ABSTRACT

Aims: Ankylosing spondylitis(AS) is the most common and characteristic form of Spondyloarthritis. The pan-immune inflammation value(PIV) is a marker obtained from complete blood count parameters, which has been used as an inflammatory and immune marker. In this study, we aimed to investigate the relationship between inflammation and disease activity in patients with AS and PIV.

Methods: In this prospective controlled study a total of 208 participants were included, consisting of 104 AS patients and 104 healthy controls. Complete blood count values, including neutrophils, monocytes, lymphocytes, platelets, and also C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were measured in all participants. In AS group disease activity was assessed with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The AS group was divided into two subgroups based on BASDAI score: low disease activity(BASDAI score <4) and high disease activity(BASDAI score ≥4).The pan-immune inflammation value of patients and the control group was calculated as neutrophil count × monocyte count × platelet count/lymphocyte count. Comparative analysis was performed between the two groups, and these values were also compared based on the BASDAI.

Results: The AS group exhibited statistically higher values of CRP, monocytes, and PIV compared to the control group (p<0.001 for all). Patients with BASDAI≥4 had a statistically lower disease duration (p<0.001) and lymphocyte count (p:0.012) compared to those with BASDAI<4. Patients with BASDAI ≥ 4 had statistically higher values of CRP, ESR, neutrophils, platelets, and PIV compared to those with BASDAI<4 (p<0.001, p<0.001, p<0.001, p:0.008, p<0.001 respectively). Strong positive correlation was found between PIV and BASDAI (rho=0.790; p<0.001), moderate positive correlation with PIV and CRP (rho=0.467; p<0.001) and also positive correlation was found between PIV and ESR (rho=0.326; p<0.001). The specificity and sensitivity of PIV using a cutoff value of >309,2 were 80.0% and 86.0% respectively, for the active group.

Conclusion: Since the parameters comprising PIV are obtained from a complete blood count, it provides an advantage for its use as a simple and cost-effective marker in ankylosing spondylitis patients. In our study, we demonstrated that PIV is sensitive and specific in differentiating disease activity in patients with ankylosing spondylitis from healthy individuals and associated with disease activity.

Keywords: Ankylosing spondylitis, pan-immune-inflammation value, disease activity

INTRODUCTION

Ankylosing spondylitis (AS) is the most common and characteristic form of Spondyloarthritis (SpA). AS is a common inflammatory disease that primarily affects the axial skeleton, sacroiliac joints and paraspinal soft tissues. It can also manifest with extra-articular symptoms such as anterior uveitis, inflammatory bowel disease, aortic valve disease, and osteoporosis, as well as peripheral joint involvement.[1,2]

While the exact pathogenesis of AS remains unclear, it is known that an inflammatory process initiated by certain environmental factors in individuals with genetic predisposition. Not only human leukocyte antigen B-27 (HLA B-27) but also the other HLA alleles like HLAB-47, HLAB-51 plays an important role in the disease. The IL-23-IL-17 pathway plays a major role in the pathophysiology of ankylosing spondylitis. Under the influence of IL-6 and TGF-β, which enhance IL-23R presentation on Th17 cells, CD4+ T cells transform into IL-17-producing Th17 cells, initiating a response to infections.[3]

It is important to diagnose the disease to prevent major complications and for early treatment. AS usually shows itself with chronic inflammatory lower back pain at the third decade of life. Along with clinical findings, a positive family history, and partially supportive laboratory tests accompanies.[4] Inflammatory lower back pain and morning stiffness are common symptoms of AS, which

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lead to activity limitation and increased pain during the active phase of the disease. Therefore, assessing disease activity in AS is crucial for better understanding the pathophysiology of AS and predicting disease prognosis. There is no specific laboratory test that can diagnose AS. Although acute phase reactants like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been used at rheumatic diseases[5] CRP has been used as a useful parameter in the follow-up of the progression of the disease. In some studies, it has been found that an increase in CRP levels is associated with radiological progression.[6] At the same time, CRP has also been a useful parameter in making treatment decisions and monitoring the response to treatment. A decrease in CRP levels in patients undergoing Tumor Necrosis Factor-alpha (TNF-α) blocking therapy may indicate that the response is better.[7] However, they are not high in all patients and do not always show disease activity. At the same time, their use is limited due to their increase in other infectious and inflammatory diseases and their more pronounced increase in peripheral involvement compared to axial involvement. Recently, hemogram parameters have been investigated as a marker of inflammation in the follow-up of various inflammatory diseases. Such as lymphocyte monocyte ratio,[8] monocyte hdl ratio,[9] systemic immune inflammation index.[10] PIV is one of these markers. Unlike SII, monocytes, which are natural cells of the immune system, also participate in the calculation of PIV therefore we think that it will be more effective in showing disease activity. Imaging methods are of great importance in the diagnosis and classification of AS.[11,12]

The pan-immune inflammation value (PIV) is a marker calculated from complete blood count parameters and is used to assess the severity of inflammation. It is confirmed that PIV will be used to evaluate the prognosis in various oncological diseases.[13] It has been shown to be associated with clinical outcomes and lymphocytes infiltrating tumors in esophageal cancer.[14] Furthermore, PIV has been reported as a promising predictor of long-term outcomes in colorectal cancer patients.[15] In another study, it was shown to have prognostic potential in breast cancer patients treated with neoadjuvant chemotherapy.[16] In a different study evaluating the relationship between survival and PIV in operated breast cancer patients, PIV was found to be significant in predicting survival.[17]

Different outcome measures have been developed to evaluate the disease activity in patients with AS. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was the first of these measures and is a six-question scale that assesses fatigue, axial involvement, peripheral joint involvement, enthesopathy, and morning stiffness. The scale is a visual analog scale with response options being "none" scored as 0 to "very severe," scored as 10. According to the Assessment in SpondyloArthritis international Society (ASAS) criteria of the international spondyloarthritis assessment group, those with BASDAI≥4 and above are considered active disease.[18-20]

In our study, we aimed to investigate the relationship between inflamation and disease activity in patients with AS and PIV

METHODS

This study was approved by Hitit University Clinical Researches Ethics Committee (Date: 03.10.2023 Decision No: 2023-130), and all protocols involving human subjects were conducted in strict accordance with ethical guidelines outlined by the institutional and/or national research governing body, the 1964 Declaration of Helsinki, and its subsequent revisions or analogous ethical criteria.

A total of 208 participants, including 104 ankylosing spondylitis patients and 104 healthy individuals, were included in our prospective controlled study. Patients with acute infections, diabetes, a history of malignancy, those using medications that could alter hemogram parameters, and those whose ankylosing spondylitis treatment had changed in the last three months were excluded. Healthy participants were selected from individuals who attended routine check-up and did not have acute or chronic infections, a history of malignancy, a history of medication use affecting hemogram parameters, acquired immunodeficiency, or pregnancy. Demographic data was recorded. Labarotory results of patients with AS and healthy individuals were examined. Hemogram parameters including neutrophils (10^9/L), monocytes (10^9/L), lymphocytes (10^9/L), platelets (10^9/L), and also CRP (mg/L) and ESR (mm/h) levels were recorded. The pan-immune inflammatory index of patients and the control group was calculated as neutrophil count × monocyte count × platelet count/lymphocyte count. In AS group disease activity was assessed with BASDAI. It is a patient reported disease activity index. Higher scores indicates the severe disease. The patient group was divided into two subgroups according to the BASDAI scores. Low activity group (BASDAI score <4) and high activity group (BASDAI score ≥4). Comparative analysis was performed between AS and control group and also for the low activity and high activity groups.

Using the G*Power program for sampling calculation, Kayhan et al.[21] calculated with the reference work of. The total number of samples was calculated with the parameters Effect size =0.51, α error probability =0.05, Power (1-β error probability) =0.95 and number of groups =2 (case/control ratio =1). According to the

results obtained, the total number of samples is 208. To calculate the minimum number of samples per group, the total number of samples was divided by the number of groups. According to this calculation, a minimum of 104 people per group will be included in the study.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as the number of units (n), percentages (%), means ± standard deviations, medians, and interquartile ranges. The normal distribution of data for numerical variables was assessed using the Shapiro-Wilk normality test. Variance homogeneity of groups was analyzed using the Levene test. The distribution of groups by gender was evaluated using the chi-square test. For numerical variables, two-group comparisons were conducted with independent samples t-tests if the data showed a normal distribution, and with Mann-Whitney U tests if the data did not exhibit a normal distribution. PIV values for control, BASDAI <4, and BASDAI ≥4 patients were compared using the Kruskal-Wallis H test. Post hoc comparisons were conducted using the Dunn-Bonferroni test. The relationship between BASDAI and the pan-immune-inflammation index was evaluated through Spearman correlation analysis.[22] The potential of the pan-immune-inflammation index to serve as a biomarker in AS groups was assessed using receiver operating characteristic (ROC) Curve analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

In this study 102 patients with AS and 102 healthy controls were evaluated. The demographic and blood parameters are presented in **Table 1**. Groups are similar in age (p:0,109) and sex. The CRP, monocyte, and PIV values are statistically higher in AS group (p<0.001, p<0.001, p<0.001 respectively). There are no statistically significant differences in the other variable values between the groups.

When patients with AS divided into two subgroups according to BASDAI there is no statistically significant difference in age and sex between low activity group and high activity group. The disease duration and lymphocyte counts of patients in the BASDAI ≥ 4 group are statistically lower. The CRP, ESR, hemoglobin, neutrophil, platelet, and PIV values of patients in the BASDAI ≥ 4 group are statistically higher (p<0.001, p<0.001, p:0.028, p<0.001, p:0.008, p<0.001 respectively) (**Table 2**).

According to the correlation analysis between BASDAI and the PIV, a statistically significant strong positive correlation was found between the two variables (rho=0.790; p<0.001) (**Figure 1**)

Table 1: Demographic and Labaratory findings of groups

	Groups		Test statistics	
	AS n=104	control n=104	Test value	p value
Age, (year)	42.2±10.4	44.5±10.5	1.611	0.109†
Sex, n (%)				
Male	59 (56.7)	59 (56.7)	-	-
Female	45 (43.3)	45 (43.3)		
CRP	6.70 (13.04)	3.22 (0.89)	3.783	<0.001&
ESR	12.0 (16.0)	9.0 (11.8)	1.837	0.066&
Hemoglobin	13.85±1.65	14.10±1.63	1.097	0.274†
Neutrophil	4.55±1.18	4.26±1.41	1.593	0.113†
Monocyte	0.60±0.11	0.48±0.16	6.630	<0.001†
Lenfocyte	2.34±0.61	2.40±0.67	0.754	0.452†
Neutrophil (%)	57.12±9.01	54.40±8.44	1.840	0.068†
Lenfocyte (%)	31.51±8.11	34.38±8.06	2.094	0.038†
Platelet	273.5 (79.0)	262.5 (98.5)	1.205	0.228&
PIV	306.6 (127.6)	195.8 (180.4)	5.633	<0.001&

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PIV: Pan-immune inflammation value, n: Number of patients, %: Percentage of columns, numerical data are given as mean±standard deviation or median (interquartile range) values. †: T test in independent samples, &: Mann-Whitney U test

Tablo 2. Comparison of variables according to BASDAI groups

	BASDAI		Test statistics	
	<4 n=60	≥4 n=44	Test value	p value
Age, (year)	41.9±11.2	42.5±9.3	0.274	0.784†
Sex, n (%)				
Male	29 (48.3)	30 (68.2)	3.306	0.069‡
Female	31 (51.7)	14 (31.8)		
Disease duration, (month)	20.5 (15.2)	6.5 (6.2)	5.848	<0.001&
CRP	3.21 (2.90)	15.00 (18.50)	6.715	<0.001&
ESR	9.0 (13.7)	19.0 (25.0)	3.515	<0.001&
Hemoglobin	13.54±1.64	14.26±1.59	2.224	0.028†
Neutrophil	4.14±0.87	5.10±1.32	4.196	<0.001†
Monocyte	0.59±0.11	0.62±0.10	1.447	0.151†
Lenfocyte	2.46±0.58	2.16±0.60	2.560	0.012†
Neutrophil (%)	56.76±8.44	57.72±10.05	0.429	0.669†
Lenfocyte (%)	32.43±7.78	29.96±8.58	1.234	0.221†
Platelet	266.5 (78.7)	285.0 (77.5)	2.649	0.008&
PIV	247.3 (99.8)	415.4 (216.1)	6.895	<0.001&

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PIV: Pan-immune inflammation value n: Number of patients, %: Percentage of columns, numerical data are given as mean±standard deviation or median (interquartile range) values. †: T test in independent samples, &: Mann-Whitney U test, ‡: Kikare test

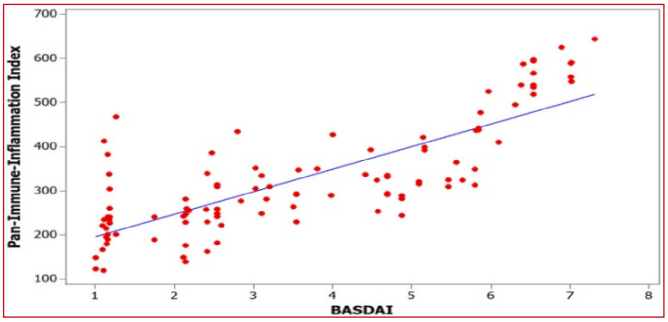

Figure 1. Graph of the relationship between BASDAI and pan-immune-inflammation value

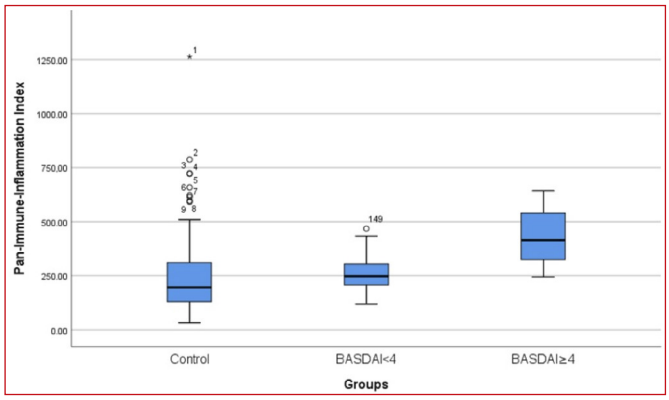

Figure 2. Pan-immune-inflammation value of the groups

There is a statistically significant difference in PIV between the control group, BASDAI <4 (p<0.001), and BASDAI ≥ 4 patients. The PIV of BASDAI ≥ 4 patients are statistically higher than those of the control group and BASDAI <4 patients (p<0.001). However, there is no statistically significant difference in PIV between the control group and BASDAI <4 patients (p:0,097) (**Table 3**).

According to the correlation analysis between CRP and PIV, a statistically significant moderate positive correlation was found between the two variables (rho=0.467; p<0.001). Also there is a statistically significant weak positive correlation was found between PIV and ESR (rho=0.326; p<0.001).

The performance of the PIV in predicting BASDAI groups was evaluated using ROC Curve analysis. According to the analysis, all areas under the curve are statistically significant, and the Pan-Immune-Inflammation Value reached the highest AUC value in the analysis for BASDAI <4 and BASDAI ≥4 groups. The obtained AUC value for distinguishing BASDAI <4 and BASDAI ≥4 patients is 0.897. When the PIV is>309.2, a sensitivity of 86.0% and a specificity of 80.0% are achieved (**Table 4**).

DISCUSSION

As our knowledge this is the first study which demonstrated that PIV levels were higher in patients with AS and correlated with disease activity. Also PIV was positively correlated with BASDAI, CRP and ESR. Ankylosing spondylitis (AS) is a common rheumatic disease characterized by chronic inflammation of the axial joints, primarily affecting the sacroiliac joints, spinal processes, and paraspinal soft tissues. The etiology of the disease is unknown. The first symptoms of the disease usually appear before the age of 30, and it predominantly affects men compared to women.[23] In our study, we also observed that the group with high disease activity had a higher number of male patients compared to female patients.

The immune system plays a crucial role in the pathophysiology of AS. Neutrophils play a role in the release of chemokines, cytokines, and growth factors, while platelets are involved in the increased levels of cytokines in inflammation. Inflammatory events lead to an increase in neutrophils, monocytes, and platelets, while lymphocyte levels decrease.[24] Various markers have been used in AS from past to present. There is not yet a definitive marker to assess systemic inflammation in patient with AS. Previously, the neutrophil lenfocyte ratio, platellet lenfocyte ratio systemic immune inflammation index have been used to indicate prognosis and disease activity in AS.[25-27] PIV is a newly developed index and includes all four main parameters of the complete blood count together neutrophil, monocyte, platelet and lymphocyte counts. PIV may be superior in demonstrating systemic inflammation compared to NLR and PLR but more studies on this issue are needed.

In our study, when the AS patient group was compared with the healthy control group, it was observed that the patient group had higher platelet and neutrophil counts and lower lymphocyte counts. Studies shown that in AS, with increasing inflammation, neutrophil and platelet

Table 3: Comparison of pan-immune-inflammation value by control and BASDAI groups

	Groups			Test Statistics		Pairwaise Comparisons		
	Control n=104	BASDAI <4 n=60	BASDAI ≥4 n=44	H value	p value	Control vs BASDAI <4	Control vs BASDAI ≥4	BASDAI <4 vs BASDAI ≥4
PIV	195.8 (180.4)	247.3 (99.8)	415.4 (216.1)	58.490	<0.001	0.097	<0.001	<0.001

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index , PIV: Pan-immune inflammation value The numerical data are given as the median (interquartile range) values. H: Kruskal-Wallis test

Table 4. Evaluation of the performance of the pan-immune-inflammation index in predicting BASDAI groups by ROC curve analysis

	AUC (95.0% CI)	p	Cutoff	Sensitivity (95.0% CI)	Specificity (95.0% CI)
Control vs AS	0.726 (0.660-0.785)	<0.001	>225.8	82.7 (74.0-89.4)	65.4 (55.4-74.4)
Control vs BASDAI<4	0.643 (0.564-0.716)	<0.001	>219.3	73.3 (60.3-83.9)	62.5 (52.5-71.8)
Control vs BASDAI≥4	0.840 (0.771-0.895)	<0.001	>243.9	100 (92.0-100.0)	69.2 (59.4-77.9)
BASDAI<4 vs BASDAI≥4	0.897 (0.822-0.948)	<0.001	>309.2	86.0 (72.6-94.8)	80.0 (67.7-89.2)

AS: Ankylosing spondylitis BASDAİ: Bath Ankylosing Spondylitis Disease Activity Index AUC: Area under the curve, CI: Confidence interval

levels increase, while lymphocyte numbers decrease, which is consistent with our findings.

In our study it was found that according to the disease activity in AS determined with BASDAI, neutrophil and platelet levels increased and lymphocyte numbers decreased in patients with increased inflammation, similar to the studies in the literature.[28] There is no clear relationship between the clinical and imaging findings of acute phase reactants such as CRP, ESR and the progression of the disease in the evaluation of disease activity in AS patients. A study conducted by Liu et al. found that neither CRP nor ESR were superior in evaluating disease activity in ankylosing spondylitis patients.[29] However, there are also studies in the literature that show a positive correlation between the disease activity of ankylosing spondylitis patients and CRP, ESR levels. In the literature review conducted by Ruof and colleagues, there are data that acute phase reactants correlate with the activity of ankylosing spondylitis patients.[30] We also observed that the CRP and ESR values of patients with high BASDAI in the patient group were higher compared to the control group.

PIV has been used mostly as a prognostic biomarker in cancer diseases in the literature obtained from complete blood count parameters.[31,32] In a meta-analysis conducted by Güven et al.[33] it was stated that PIV may be a prognostic biomarker in cancer. A study conducted with peritoneal dialysis patients found that the initial PIV was significantly associated with an increased risk of death due to all causes, cardiovascular diseases and infection.[34] In a retrospective study conducted in patients with membranous nephropathy, it was found that PIV is a reliable marker for predicting a non-remission state.35 PIV was studied at some rheumatological diseases, rheumatoid arthritis,[36] antineutrophil cytoplasmic antibody-associated vasculitis (AAV), familian mediterrenean fever (FMF). Tutan et al.[37] found an association between PIV and disease activity at romatoid artritis. Lee et al.[38] found an association between worse prognosis and high PIV levels in patients with AAV. In the previous study in FMF, patients were groupped as FMF gene mutations PIV were found higher in all groups but they foun no difference between the groups.[39]

In our study, it was also found that the patients' PIV level was sensitive and specific when the disease activity of their patients was high (BASDAI ≥4). Again, we found in our study that PIV significantly correlated with increased CRP and ESR levels in ankylosing spondylitis patients during periods when their diseases are active.

Since PIV contains parameters that play a role in immunity and inflammation, we tried to show in our study that it can be a biomarker that can indicate inflammation in chronic diseases. We think that with PIV we can get information about the disease activity of patients just by looking at the complete blood count. PIV is simple, low-cost and easy to access in routine clinical settings compared to the other serum markers.

The assessment of disease activity in AS is challenging, and also its is important because we decide on treatment according to disease activity and evaluate response to treatment. However, acute-phase reactants like CRP and ESR are often used to monitor the disease and treatment response. In our study, when looking at the BASDAI level of the patient group, it was observed that the CRP and ESR values of patients with high BASDAI were higher than those in the control group. And also PIV is associated with BASDAI, CRP and ESR levels.

Our results demonstrated that PIV levels were significantly higher in AS patients with high disease activity (BASDAI ≥4). PIV showed high sensitivity and specificity in distinguishing AS patients with high disease activity from those with low disease activity. This suggests that PIV can be a valuable marker for assessing disease activity in AS. In the previous study in patients with RA, PIV is associated with disease activity as our study.

Limitations

The medications used by patients with AS and their effect on PIV were not evaluated in our study. In addition, patients were evaluated once and the relationship between disease activity and PIV was not investigated in long-term follow-up.

CONCLUSION

One of the key advantages of PIV is that the parameters used to calculate are obtained from a simple and inexpensive complete blood count. According to our study, PIV can be a useful marker for assessing disease activity in ankylosing spondylitis, especially in patients with high disease activity and those who may not have access to more specialized tests. PIV may provide a valuable tool for clinicians to monitor and manage AS patients more effectively. However, further research and validation in larger and diverse populations are needed to confirm its clinical utility.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval was obtained from Hitit University Clinical Researches Ethics Committee (Date: 03.10.2023 Decision No: 2023-130).

Informed Consent

Written consent was obtained from the patient participating in this study.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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